COVID-19

Amid the cheering, some vaccines face questions

A candidate from AstraZeneca and the University of Oxford has puzzling efficacy data

By Jon Cohen

The drumbeat of good news about COVID-19 vaccines has continued, albeit with some dissonant notes. By now four makers have reported results ranging from encouraging to stunningly positive from phase III clinical trials. The announcements, delivered by press release, have left scientists hungering for more data, but have persuaded many that a safe and effective vaccine against SARS-CoV-2, the pandemic coronavirus, has moved from a question of if to when and how. “It’s very good to have positive results from different platforms,” says Ana Maria Henao Restrepo, who leads an effort at the World Health Organization to stage COVID-19 vaccine comparisons.

At the same time, two of the four COVID-19 vaccines face more questions than the other pair. AstraZeneca and the University of Oxford promoted their candidate, which uses an adenovirus to deliver the gene for the spike protein of SARS-CoV-2, as being nearly as protective as vaccines from Moderna and Pfizer and BioNTech. Those vaccines, which rely on messenger RNA (mRNA) to deliver the genetic code for spike, prevented symptomatic disease with 95% efficacy and appeared to block serious COVID-19 almost entirely.

But the AstraZeneca/Oxford announcement last week came from an interim analysis blending two trials of the vaccine in which people received different doses—apparently by accident. Efficacy ranged from 62% to 90%, depending on the dosing strategy. Meanwhile, Russia’s Gamaleya Research Institute of Epidemiology and Microbiology, which also uses adenoviruses as vectors to deliver spike’s gene, claimed 91.4% efficacy based on a second interim analysis of its candidate, Sputnik V. But that rested on far fewer COVID-19 cases than Moderna or Pfizer and BioNTech reported and the Gamaleya trial is still ongoing.

The AstraZeneca/Oxford effort conducted initial efficacy trials in the United Kingdom and Brazil. Science has learned from a scientist working with the partner-ship who asked not to be named that a calculation error early in the U.K. study led to vaccine vials being filled with half the intended dose. Rather than drop people who had already received that shot, the team modified the trial protocol to compare people who received a half dose followed by a full dose with those given two full doses.

An AstraZeneca official acknowledged the half dosing was a mistake, but Oxford researchers challenged this, and neither side would respond to requests to further discuss the issue. “It’s a head scratcher on a number of levels, and this is the worst aspect of AstraZeneca and Oxford used the same adenovirus vector for both shots, which could explain why the larger boost dose produced the weaker result in its trial. “I would bet on that being a contributor, but not the whole story,” says Adrian Hill, director of Oxford’s Jenner Institute, which designed the vaccine.

Moore says the vaccines’ versions of the spike protein may also matter. In nature, viral surface proteins can “wobble.” His group in 2002 added stabilizing mutations to HIV’s surface protein, which other groups later showed led to more robust antibody responses when it was injected into animals. Moderna, Pfizer and BioNTech, and other COVID-19 vaccine makers have added similar mutations to spike. Hill’s team did not. “Oxford is out on a limb,” Moore says.

In the United States, Warp Speed has enrolled about 11,000 of a planned 40,000 participants in a third efficacy trial of the AstraZeneca/Oxford vaccine that uses the full-dose prime. The study may obtain an efficacy signal before being fully enrolled or it could switch to a half-dose prime, Slawoi adds, if researchers tease out the factors that led to 90% protection.

Henao Restrepo says it’s important to factor in that the AstraZeneca/Oxford vaccine is relatively cheap, about $3 per dose, and only needs refrigeration temperatures for storage. The mRNA vaccines will cost at least $20 per dose and must be kept at subzero temperatures. AstraZeneca also says it can produce at least 3 billion doses next year, far more than projections from any other manufacturer.

A U.S. Food and Drug Administration vaccine advisory group plans to publicly review applications for emergency use authorization from Pfizer and BioNTech on 10 December and from Moderna 1 week later. The candidate from Pfizer and BioNTech appears poised to receive similar U.K. authorization as soon as this week.

But Hill says the COVID-19 vaccine race isn’t over. “If we provide more vaccine next year, particularly in places where there’s a lot of disease like Brazil and India, and save more lives, that’s winning to us—not having done the press release first,” he says. ■
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